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METHOD FOR TREATING RESPIRATORY DISTRESS SYNDROME

This invention relates to the therapy of respiratory distress syndrome. In particular, it relates to novel methods for the use of lung surfactants in the treatment of respiratory distress.

Neonatal respiratory distress syndrome (RDS), also known as hyaline membrane disease, is a major cause of morbidity and mortality of the prematurely born infant. It has been estimated that almost 20% of infants born at 30-32 weeks gestational age and between 60 and 80% of infants born at 26-28 weeks gestational age will develop RDS (Jobe, *et al.*, Am. Rev. Resp. Dis. 136:1256, 1987). RDS currently leads to the death of approximately 5000 infants annually in the United States (Wegman, Pediatrics 74:981, 1984). Many RDS-afflicted infants will survive, but suffer with major medical complications including chronic lung disease (bronchopulmonary dysplasia) and neurological defects.

RDS in the premature infant is believed to be caused primarily by a deficiency of lung surfactant -- a lipid-protein mixture which coats the airspaces of the lung -- thereby reducing the surface tension and preventing airspace collapse. The principal component of lung surfactant -- dipalmitoylphosphatidylcholine (DPPC) -- was identified several years ago (Klaus, *et al.*, Proc. Natl. Acad. Sci. USA 47:1858, 1961; Avery, *et al.*, Am. J. Dis. Child. 97:517, 1959).

However, results of clinical trials using DPPC alone were disappointing. Aerosol administration of DPPC alone to infants with RDS did not lead to any benefit (Robillard, *et al.*, Can. Med. Assoc. J. 90:55, 1964; Chu, *et al.*, Pediatrics 40:709, 1967).

The literature contains numerous different lung surfactant preparations, including those with DPPC plus other components, which have been examined in clinical trials, with varying apparent benefit in the treatment of RDS (Jobe, *et al.*, Am. Rev. Resp. Dis. 136:1256, 1987). Fujiwara, for example, reported improved gas exchange in infants with RDS who were treated with a modified bovine surfactant (Fujiwara, *et al.*, Lancet 1:55, 1980).

Generally, preparations can be classified into five types. These include 1) natural human surfactant (purified from human amniotic fluid), (Merritt, *et al.*, N. Engl. J. Med. 315:787, 1986,) 2) semisynthetic surfactant (prepared by combining DPPC and high density lipoprotein), (Halliday, *et al.*, Lancet 1:476, 1984) 3) animal lung surfactant (isolated by organic extraction of the whole lung or lavage fluid), (Fujiwara, *supra*; Enhorning, *et al.*, Pediatrics 76:145, 1985; Kwong, *et al.*, Pediatrics 76:585, 1985) 4) purified human surfactant apoproteins (SP-A, SP-B, and/or SP-C purified from natural sources or derived by recombinant DNA technology; see Jobe *et al.*, Am. Rev. Resp. Dis. 136:1032, 1987, and Glasser *et al.*, J. Biol. Chem. 263:10326, 1988) which are reconstituted with surfactant lipids (Revak, *et al.*, J. Clin. Invest. 81:826, 1987) and 5) protein-free synthetic surfactants prepared using either a mixture of DPPC and phosphatidylglycerol, or a mixture of DPPC, tyloxapol, and hexadecanol (Morley, *et al.*, Lancet 1:64, 1981; Durand, *et al.*, J. Pediatrics 107:775, 1985).

The literature discloses references to the timing and mode of administration of surfactant preparations. All published animal and human studies to date have administered lung surfactant after birth, using either "rescue" or "prophylactic" protocols.

Many of the clinical studies were "rescue" protocols, in which the only treated infants were those who had already developed signs and symptoms of RDS requiring tracheal intubation and mechanical ventilation. The clinical results of this approach were highly variable (e.g. Gitlin, *et al.*, Pediatrics 79:31, 1987). Many infants showed minimal or no improvement in gas exchange and lung mechanics. Moreover, frequently the beneficial effects were not observed until more that an hour had passed and the improvement was often shortlived.

A number of animal models of RDS exist which appear to be relevant to the human disease. Animal studies in rabbits, lambs and baboons have supported the concept that surfactant treatment soon after birth is more effective than late surfactant treatment (Nilsson, *et al.*, Pediatr. Res. 12:249, 1978; Jobe, *et al.*, J. Appl. Physiol. 55:169, 1983; Maeta, *et al.*, Pediatrics 81:277, 1988).

Because of these considerations and the high incidence of RDS in very premature infants (less than 30 weeks gestation), clinical studies were initiated to examine "prophylactic" adminstration of exogenous surfactant, i.e., after birth and before the first breath (Enhorning, *et al.*, Pediatrics, 76:145, 1985; Merritt, *et al.*, N. Engl. J. Med., 315:785, 1986).

Although the first clinical studies of prophylactic administration, namely of exogenous lung surfactant to very premature infants, showed significant efficacy as measured by greatly reduced mortality (Merritt, *et al.*, *supra*), subsequent studies have shown marginal benefits (Soll, *et al.*, Pediatr. Res. 23:425A, 1988; Kendig, *et al.*, Pediatr. Res. 23:413A, 1988).

Maeta, *supra*, suggests that the timing and method of instillation of surfactant could be reasons for the observed variation in response. Physicians performing these studies have described great technical difficulty in actually achieving administration of lung surfactant after birth but before the first breath. A recent trial of "prophylactic" adminstration has therefore been modified to administer surfactant within 15 minutes of birth, rather than before the first breath (Soll, *et al.*, Pediatr. Res. 23:425A, 1988, Presentation at the Annual Meeting of The American Pediatric Society and The Society of Pediatric Research).

Currently practiced methods of administration remain unsatisfactory. Many of the complications of RDS develop as a consequence of the high inflation pressures and high concentrations of inspired oxygen required to mechanically ventilate the lungs of infants who exhibit signs and symptoms of RDS (Perelman, Seminars in Perinatology 10:217, 1986). Even those newborns who respond most dramatically to surfactant administration after birth require mechanical ventilation with high inflation pressures and high inspired oxygen concentrations for some period of time. High inflation pressures and high levels of inspired oxygen contribute directly to the development of barotrauma (pneumothorax), lung injury

(epithelial necrosis and oxygen toxicity), and subsequent bronchopulmonary dysplasia and/or death.

Additionally, very soon after birth in RDS, proteins and inflammatory cells accumulate in the airspaces. Although early reports suggested that only specific proteins were capable of inhibiting surfactant function, more recent studies suggest that most of the common serum proteins inhibit surfactant function (Seeger, *et al.*, J. Appl. Physiol. 58:326, 1985). Also, inflammatory cells and their mediators accumulate in the airspaces early in RDS and may contribute to lung injury and complicate the clinical syndrome. It has been noted that an increased concentration of surfactant can counteract inhibition by albumin (Holm, *et al.*, Chem. Phys. Lipids 38:287, 1985). Nevertheless, previous workers in the field have not developed formulations of surfactant which are specifically designed to resist protein inhibition, nor have formulations been suggested which include agents known to inhibit the activity of inflammatory cells and mediators.

Furthermore, surfactant which is administered after birth may not be distributed evenly throughout the lungs. Most commonly, surfactant is taken up as an emulsion into a syringe and is administered directly into the lungs of a patient through an endotracheal tube. To facilitate even distribution throughout the lungs, surfactant is typically administered in several aliquots with the patient turned in different positions for each administration. Results from animal and human studies suggest that uneven distribution may be a serious problem with the current methods for surfactant administration. Robertson and Enhorning administered a suspension of concentrated natural surfactant mixed with iron-dextran to premature rabbits, and observed an uneven distribution (Pediatrics, 50:58, 1972). Uneven distribution has also been suggested by reports of infants who have shown unilateral improvement on their chest radiographs (Fujiwara, *supra*; Edwards, *et al.*, Radiology 157:329, 1985).

Moreover, administration of surfactant to the newborn after birth subjects the infant to many avoidable iatrogenic complications. Administration of surfactant after birth typically requires the placement of an endotracheal tube, hand-bagging, and a period of mechanical ventilation using a pressure-regulated respirator. Risks associated with these procedures include, but are not limited to, improper placement of the endotracheal tube, barotrauma secondary to excessive pressures during bagging or mechanical ventilation, lung overdistension and cardiac compromise if lung compliance improves with therapy and the ventilator delivers excessive volumes, as well as the risks of infection, tracheal stenosis, bronchopulmonary dysplasia and even death from mechanical failure (Perelman, *supra*). Moreover, abrupt changes in the cardiovascular system and in the ventilatory requirements may also contribute to other complications, including brain hemorrhage and necrotizing colitis (Lipscomb, *et al.*, Lancet 1:414, 1981). In addition, it is possible that bolus administration of several milliliters of a surfactant suspension into the lungs of a very premature infant after birth could, by simple physical obstruction, actually impair ventilation to some areas of the lung.

Fetal delivery of an agent may be accomplished through intraamniotic or transamniotic administration.

Intraamniotic administration of an agent comprises the insertion of that agent into the amniotic cavity, typically by a thin needle. This procedure *per se* is widely known to practitioners, and has been used both for analytical and therapeutic purposes.

Amniocentesis is the insertion of a needle into the amniotic cavity in order to remove a small amount of amniotic fluid for analysis. The combined use of ultrasonography and a thin needle have made amniocentesis remarkably safe for both the mother and the fetus (Picker *et al.*, Aust. N. Z. J. Obstet. Gynec. 19:83, 1979). Amniocentesis is commonly performed in preterm labor to assess fetal lung maturity and to determine the risk of RDS. Measurement of lung surfactant, which is produced in the alveoli of the mature fetus and found in amniotic fluid, has predictive value in estimation of the risk of RDS (Gluck, *et al.*, Am. J. Obstet. Gynec., 109:440, 1971).

Insertion of a needle into the amniotic cavity for treatment purposes has been shown to be a convenient and effective method for delivering therapeutic agents. The most common approach has been to insert a needle through the abdominal wall of the mother into the amniotic cavity. By this route in both animal and human studies, hypertonic saline and prostaglandins have been injected in order to induce therapeutic abortions (Bygdeman, Obstet. Gynecol. 52:424, 1978), thyroid hormone has been injected in order to induce lung maturity in the fetus (Mashiach, *et al.*, J. Perinat. Med. 7:161, 1979), and bicarbonate has been injected to treat fetal acidosis (Hamilton, *et al.*, Am. J. Obstet. Gynecol. 112:834, 1972). Similarly, antibiotics have been administered into the amniotic cavity after premature rupture of the membranes by insertion of a needle through the cervical canal (Ogita, *et al.*, Am. J. Obstet. Gynecol. 158:23, 1988).

It has been shown that ^{51}Cr-labeled red cells injected into the amniotic cavity of pregnant women accumulated diffusely throughout the lungs of the fetus within hours after administration (Duenhoelter, *et al.*, Obstetrics and Gynecology 43 (6):878, 1974; Duenhoelter, *et al.*, Obstetrics and Gynecology 42:746, 1973).

In addition, the presence of lung surfactant in the amniotic fluid has been reported to lubricate the amniotic membranes, helping to avoid premature rupture of the membranes and premature delivery, Hills, *et al.*, Am. J. Ob. Gyn. 149:896, 1984.

Transamniotic administration comprises the delivery of a therapeutic agent directly to the fetus. This procedure per se is also widely known to practitioners. It has been used, for example, for intrauterine fetal blood transfusion therapy by injection into the fetal peritoneal cavity (Birnholz, *et al.*, N. Engl. J. Med. 304:1021, 1981). However, transamniotic administration of a drug directly into the lungs of a fetus by "fetobronchoscopy" has not been described.

It is an object of this invention to provide an effective therapy for human or other animal patients suffering from deficient lung surfactant and neonatal respiratory distress syndrome.

It is a further object of this invention to provide a means of preventing the occurrence of neonatal respiratory distress syndrome.

It is an additional object of this invention to minimize the side effects of surfactant therapy in the treatment of respiratory distress syndrome.

It is another object of this invention to minimize the occurrence of neonatal respiratory distress syndrome by lubricating the walls of the amniotic cavity to prevent premature rupture of the membranes and premature delivery.

It is another object of this invention to increase the therapeutic efficacy of lung surfactant *in vivo*.

The objects of this invention are accomplished by a method comprising treating a patient at risk for respiratory distress syndrome by the fetal delivery of a therapeutically effective dose of lung surfactant. In one embodiment, this is accomplished through intraamniotic administration before delivery. This method ensures that the surfactant is evenly distributed throughout the lungs before the first breath. In another embodiment, transamniotic administration delivers surfactant directly to fetal lungs. The administration may desirably be timed so that breathing efforts in utero which are present as early as about 20 weeks of gestation (Natale, et al., Am J. Obstet Gynecol. 158:317, 1988) facilitate movement of the surfactant into the lungs of the fetus. Fetal delivery may be accomplished while in the mother's womb, or in any environment or container where the fetal lungs communicate with surrounding fluid.

Surfactant as defined herein means any composition, including lipids and/or proteins, which is capable of lowering the surface tension at air-liquid interfaces in the lung. This definition encompasses lung surfactant, as described above, together with its amino acid, glycosylation and other variants or derivatives. The literature discussed *supra* describes suitable lung surfactant preparations. It is expected that other surfactant variants and derivatives will become available in the future, and these are to be considered to fall within the scope of this invention.

Surfactant is prepared by known methods from synthetic dipalmitoylphosphatidylcholine (DPPC), egg or synthetic phosphatidylglycerol (PG), and purified surfactant apoproteins (SP-B and/or SP-C and/or SP-A). Purified surfactant apoproteins are obtained by recombinant methods or direct synthesis using published nucleotide and amino acid sequences (Glasser, *et al.*, Proc. Natl. Acad. Sci. U.S.A. 84:4007, 1987; Jacobs, *et al.*, J. Biol. Chem. 262:9808, 1987; Floros, *et al.*, J. Biol. Chem. 261:9029, 1986; White, *et al.*, Nature 317:361, 1985; Whitsett, *et al.*, Pediatr. Res. 19:501, 1985; Warr, *et al.*, Proc. Natl. Acad. Sci. U.S.A. 84:7915, 1987; Hawgood, *et al.*, Proc. Natl. Acad. Sci. U.S.A. 84:66, 1987; Glasser, *et al.*, J. Biol. Chem. 263:9, 1988, Glasser, *et al.*, *supra*, J. Biol. Chem. 263:10326, 1988; and Jobe *et al.*, Am. Rev. Resp. Dis. 136:1032, 1987). Desirably, surfactant apoproteins are reconstituted with surfactant lipids, Revak, *supra*.

Purified surfactant apoproteins may also be obtained from amniotic fluid, human or animal, or from cell culture, using cells which naturally produce these molecules. Surfactant is also obtained by isolation of natural surfactant from human or animal amniotic

fluid. Alternatively, surfactant may be isolated by known methods--e.g. by organic extraction of lung tissue or by lavage from human or animal lung, and then supplemented with phospholipids, as desired. Protein-free synthetic surfactant (Morley, *supra*; Durand, *supra*) and any other composition capable of lowering surface tension at the air-liquid interface in the lungs (e.g. McIver, *et al.*, Biochm. Biophys. Acta 751:74, 1983) are encompassed within the scope of this invention. Surfactant from other animal species can be used in the treatment of human respiratory distress syndrome, and vice versa.

Surfactant for fetal delivery is placed into sterile, isotonic formulations together with required cofactors. The formulation of surfactant is preferably liquid, and is ordinarily a physiologic salt solution containing 0.5 - 10 mM calcium, non-phosphate buffer at pH 6.8-7.6. Saline is a suitable carrier, although other conventional parenteral solutions or buffers are usable. The final concentration of surfactant in solution is typically about 10-40 mg/ml, in generally about 0.5 - 30 ml.

Surfactant may be provided as lyophilized powder for ultimate delivery in solution, or the powder may be encapsulated and inserted into the amniotic cavity through the cervix or by surgical means. Surfactant can be administered from sustained release compositions, for example as polylactide or polyhydroxylbutyrate implants or liposomes such as are described in EP 17,2007A, or by continuous infusion.

Surfactant also is suitably formulated with other pharmacologic agents in order to modify or enhance the half-life, the distribution, or the therapeutic activity of the surfactant. These pharmacologic agents may be administered separately to the mother, reaching the fetus via the placenta, or may be coadministered intraamniotically or transamniotically. Agents which increase the fetal inspiration of amniotic fluid are suitable for coadministration; for example, maternal administration of glucose has been shown to increase fetal breathing activity (Lewis, *et al.*, Br. J. Obstet. Gynecol. 85:86, 1978). Drugs which increase fetal breathing activity or reduce laryngeal contraction and obstruction of the tracheal inlet such as catecholamines may be coadministered (Murata, *et al.*, Am. J. Obstet. Gynecol. 139:942, 1981). In addition, drugs which reduce the production of fetal pulmonary fluid may facilitate distribution of lung surfactant into the fetal lungs. For example, arginine vasopressin and arginine vasotocin, and catecholamines suppress tracheal secretion (Perks, *et al.*, Chest 81:63, 1982; Ross, *et al.*, Am. J. Obstet. Gynecol. 150:421, 1984; Walters, *et al.*, Pediatr. Res. 12:239, 1978). Additional pharmacologic agents suitable for coadministration include those which alter fetal swallowing and may improve distribution of lung surfactant into the lung and/or prolong its half-life.

The surfactant formulations may contain agents such as unsaturated or saturated fatty acids, and triglycerides previously suggested for use in surfactant dosage forms (Tanaka, *et al.*, Chem. Pharm. Bull. 31:4100, 1983).

Surfactant optionally is administered together with other agents or therapies heretofore employed in the therapy of respiratory distress syndrome. Therapies or agents which are used optionally in a course of therapy with fetal delivery of surfactant include, for example, an interferon (including gamma interferon), corticosteroids, thyroid hormone,

tocolytics, relaxin, male and female sex hormones, prolactin, insulin, insulin-like growth factor-1, and growth and/or differentiation factors which could induce differentiation of type II cells in fetal lungs and/or increase their surfactant production, such as epithelial growth factor, transforming growth factor beta, or colony stimulating factors. See, for example, Whitsett, *et al*., J. Biol. Chem. 262:7908 (1987). Other agents include vitamin E, superoxide dismutase, alpha-1-antitrypsin and other antiproteases, selenium, vitamin A, antibiotics, immunoglobulins, and antiviral agents. These other agents or therapies are used at the same time as surfactant is administered or in a sequential course of therapy.

In one preferred embodiment, surfactant is formulated by a modification of the method of Revak, *supra*. Briefly, surfactant apoproteins (SP-B and/or SP-C, alone or in combination with SP-A, dissolved in chloroform) and phospholipid (in chloroform) are combined. The mixture is vortexed and dried, and resuspended in a suitable carrier solution, such as 150 mM saline with 1.5 mM $CaCl_2$. The final ratio of protein to lipid desirably ranges from 1:99 to 15:85.

The therapeutically effective dosage of surfactant to be employed by fetal delivery generally will range about from about 5-900 mg per administration, although the dose of the surfactant employed will be dependent upon the properties of the surfactant employed, e.g. its activity and biological half-life, the concentration of the surfactant in the formulation, the rate of dosage, the clinical tolerance of the patients involved, the pathological condition of the patients and the like, as is well within the skill of the physician. It will be appreciated that the practitioner will adjust the therapeutic dose in line with clinical experience for any given surfactant.

Fetal surfactant administration desirably is used after the measurement of lung surfactant in amniotic fluid reveals a deficiency, or it is used on a prophylactic basis where labor has begun prematurely. Typically, surfactant is administered to a fetus between about 20 and 44 weeks of gestation.

Additional doses of surfactant may be administered, before and/or after delivery. Since the half-life of other proteins in amniotic fluid is approximately 24 hours (Gitlin, *et al*., Am. J. Obstet. Gynecol. 113:632, 1972), additional doses may be given every 12 to 48 hours, before and/or after delivery, unless a sustained-release formulation is employed. Surfactant may be delivered to the lungs of the fetus transamniotically as shown in Example 2 below, and/or to an infant after birth by conventional direct installation after placement of an endotracheal tube. Surfactant may be delivered after birth by aerosol, using alternatively a dry power aerosol, a liquid aerosol generated by ultrasonic or jet nebulization, or a metered dose inhaler, again avoiding the complications of endotracheal tube placement.

The Examples below illustrate two embodiments of this invention, namely intraamniotic and transamniotic administration of surfactant. It should be understood that these Examples are for illustrative purposes only, and are not to be construed as limiting this invention in any manner.

EXAMPLE 1

A woman who enters labor prematurely is admitted, monitored, and given therapeutic agents to diminish uterine contractions. An evaluation of fetal age and maturity is performed. According to known methods, usually with the maternal bladder filled, sonography is used to determine the gestational age and to locate the placenta and an appropriate puncture site. The abdomen is prepped with antiseptic solution. After injection of 1% lidocaine or the like into the abdominal wall as a local anesthetic, a 20- or 22-gauge spinal needle, 3 to 6 inches long, is inserted into the amniotic cavity under ultrasonic guidance. The stylette is removed and the first 1 to 2 ml of amniotic fluid is discarded. A small amount of fluid is removed for analysis. Then, the surfactant solution (prepared from synthetic DPPC, egg phosphatidylglycerol (PG) and apoprotein SP-C, as described above) is administered by syringe injection over 1 - 5 minutes. Alternatively, the surfactant solution is rapidly injected in order to obtain more rapid distribution. A dose of 20 - 900 mg is administered. The mother may be asked to move into different positions in order to obtain more rapid distribution of surfactant throughout the amniotic fluid. Depending on the course of labor, surfactant may be readministered into the amniotic cavity.

EXAMPLE 2

A woman who enters labor prematurely is admitted, monitored, and if indicated, given therapeutic agents to diminish uterine contractions. An evaluation of fetal age and maturity is prepared. Within the scope of normal obstetrical practice amniocentesis is performed under ultrasonic guidance. A small amount of amniotic fluid is removed and analyzed. If delivery is imminent, or if there has been premature rupture of the membranes and loss of amniotic fluid, it may not be preferable to administer surfactant into the amniotic fluid. In such a situation, it is preferable to administer surfactant by transamniotic administration directly into the trachea of the fetus, using a "fetobronchoscope." For example, an instrument such as a thin flexible fiberbronchoscope (or chip bronchoscope) is sterilized and then introduced by a percutaneous transabdominal technique, under local anesthesia and with ultrasound guidance (Hobbins, *et al.*, Am. J. Obstet. Gynecol. 118:1069, 1974). Alternatively, if a caesarian section is being performed to deliver the infant, the endoscope may be introduced into the amniotic cavity by exposing the uterus by laparotomy and inserting the instrument through the myometrial incision. The endoscope is then maneuvered into the oral cavity of the fetus, through the larynx, and into the trachea. At that point, lung surfactant is instilled directly into the lungs of the fetus. A dose of 5-300 mg is administered. Depending on the course of labor, surfactant may be readministered. Additional surfactant may be administered to the lungs of the infant after delivery.

Claims

I claim:

1. A method for the treatment of a fetus having or at risk for respiratory distress syndrome, comprising delivering to the fetus a composition containing a therapeutically effective dose of surfactant.

2. The method of Claim 1 wherein the surfactant is delivered intraamniotically.

3. The method of Claim 1 wherein the surfactant is delivered transamniotically.

4. The method of Claim 1 wherein the therapeutically effective dose is about from about 5 to 900 mg per administration.

5. The method of Claim 1 wherein the therapeutically effective dose is about from about 20 to 900 mg per administration.

6. The method of Claim 1 wherein the therapeutically effective dose is about from about 5 to 300 mg per administration.

7. The method of Claim 1 wherein the surfactant is human lung surfactant.

8. The method of Claim 1 wherein the surfactant is mammalian, non-human lung surfactant.

9. The method of Claim 1 wherein the surfactant is synthetic.

10. The method of Claim 1 wherein the surfactant comprises SP-A.

11. The method of Claim 1 wherein the surfactant comprises SP-B.

12. The method of Claim 1 wherein the surfactant comprises SP-C.

13. The method of Claim 1 wherein the surfactant comprises SP-A and SP-B.

14. The method of Claim 1 wherein the surfactant comprises SP-A and SP-C.

15. The method of Claim 1 wherein the surfactant comprises SP-A and SP-B and SP-C.

16. The method of Claim 1 wherein the surfactant comprises SP-B and SP-C.

17. The method of claim 1 wherein the composition includes at least one additional composition, selected from the group consisting of an interferon, corticosteroids, thyroid hormone, tocolytics, relaxin, male and female sex hormones, prolactin, insulin, insulin-like growth factor-1, growth and differentiation factors which induce differentiation of type II cells in fetal lungs, epithelial growth factor, transforming growth factor beta, colony stimulating factors, vitamin E, superoxide dismutase, alpha-1-antitrypsin, antiproteases, selenium, vitamin A, antibiotics, immunoglobulins, and antiviral agents.

18. The method of Claim 1 wherein the fetus is thought to be at risk for respiratory distress syndrome but has not been diagnosed as having respiratory distress syndrome.

19. The method of claim 1 wherein the surfactant is administered between 20 and 44 weeks of gestation.

PATENT COOPERATION TREATY

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

issued pursuant to PCT Article 17(2)(a) (1)

IDENTIFICATION OF THE INTERNATIONAL APPLICATION	APPLICANT's OR AGENT's FILE REFERENCE
International Application No. PCT/US 90/01410	International Filing Date 12th March 1990
Receiving Office PCT/US	Priority Date Claimed 31st March 1989
Applicant (Name) GENENTECH, Inc.	

DECLARATION

This International Searching Authority hereby declares that no international search report will be established on the above-identified international application for the reasons indicated below.(1)

1. The subject matter of the international application relates to:(2)

a. [X] scientific theories.

b. [X] mathematical theories.

c. [ ] plant varieties.

d. [ ] animal varieties.

e. [ ] essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.

f. [ ] schemes, rules or methods of doing business.

g. [ ] schemes, rules or methods of performing purely mental acts.

h. [ ] schemes, rules or methods of playing games.

i. [X] methods for treatment of the human body by surgery or therapy.

j. [ ] methods for treatment of the animal body by surgery or therapy.

k. [ ] diagnostic methods.

l. [ ] mere presentations of information.

m. [ ] computer programs for which this International Searching Authority is not equipped to search prior art.

2. The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:(3)

a. [X] the description.

b. [X] the claims.

c. [ ] the drawings.

Classification: A61K37/00

comment:

CERTIFICATION

International Searching Authority	Date of Mailing	Authorized Officer
ISA / EP	01. 06. 90	T.K. WILLIS

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